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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,423	12/23/2003	Sarah L. Bolt	604-704	9858

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,423	BOLT ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/03, 4/26/04, 6/15/04 & 12/5/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/988,925.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/23/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment's filed 12/23/03, 4/26/04, 6/15/04 and Applicant's response filed 12/5/05 are acknowledged and have been entered.

2. Applicant's election of Group III (claim 27), directed to a method of treatment of a patient requiring immunosuppression, said method comprising administering an aglycosylated IgG anti-CD3 antibody to a patient in Applicant's response filed 12/5/05 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Accordingly, claims 1-26 (non-elected Group I) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim 27 is currently being examined to the extent it reads upon administering an aglycosylated IgG anti-CD3 antibody to a patient requiring immunosuppression.

It is requested that Applicant amend claim 27 to delete the limitations "having cancer or" and "of a ligand" that belong to non-elected Groups IV and V.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the declaration claims priority to application serial number *09*/988,925, filed March 9, 1993. The parent application listed in the first line of the specification is *07*/988,925, filed 11/8/93.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of treating a patient requiring any form of immunosuppression, said method comprising administering an aglycosylated IgG anti-CD3 antibody or fragment thereof, including either antigen binding or non-antigen binding fragments thereof.

The instant claim encompasses administration of an antibody fragment that does not bind antigen in order to treat a patient requiring immunosuppression, and it also encompasses treating a patient requiring any type of immunosuppression with an IgG anti-CD3 antibody or fragment thereof. There is insufficient disclosure in the specification on such a method.

The specification discloses that rodent CD3 antibodies have been used to influence immunological status by suppressing, enhancing or re-directing T cell responses to antigens, and therefore have therapeutic potential in the human for use as an immunosuppressive agent, for example, for the treatment of renal, hepatic and cardiac allografts (page 2 at lines 18-23). The specification discloses that first dose response, induced by anti-CD3 antibody administration causes elevated levels of circulating cytokines associated with CD3 antibody induced T cell activation (page 2 at lines 23-35). The specification discloses that aglycosylation of antibodies has been described to reduce their ability to bind to Fc receptors *in vitro* in some cases, but that it is not predictable that this will be true of all antibodies (page 3 at lines 11-20). The specification discloses that it is possible to produce aglycosylated CD3 antibodies of the IgG class that retain their antigen binding specificity and do not induce T cell mitogenesis *in vitro* and induce a reduced level of cytokine release *in vivo*, while still maintaining some Fc binding ability (page 3 at lines 25-30). The specification discloses that an aglycosylated IgG1 anti-CD3 antibody was less potent in eliciting TNF production

in CD3ε transgenic mice than the glycosylated antibody. However, "the mitogenicity of an antibody cannot be predicted in a straight forward fashion from the results of assays which measure Fc-Fc receptor interactions... the inability to bind to Fcγ receptors is no guarantee that an antibody will not be mitogenic" (Example 5 on pages 23-24).

The specification does not disclose what immunosuppressive condition can be treated except for transplantation rejection.

Evidentiary reference Anasetti *et al* (J. Exp. Med. 172, 12/1990, pages 1691-1700) teach that non-mitogenic IgG anti-CD3 antibody was cable of inducing specific nonresponsiveness in unprimed human T cells, but not in memory T cells (especially abstract and last paragraph of article.)

Evidentiary reference Paul (Fundamental Immunology 2nd Edition, Raven Press, 1989, paragraph spanning pages 904-905) teaches that anti-CD3 mAb OKT3 which has been used extensively in humans eliminates all T cell function, but other mAbs such as CAMPATH, T-12 and CBL1, also used in clinical trials, have not proved as effective. Paul further teaches that OKT3 administration has been effective in reversing acute rejection episodes, but demonstrates problems in terms of not always eliminating the target T cell population. Paul teaches that the use of the OKT3 antibody represents an extremely broad, nonspecific form of immunosuppression that renders the recipient broadly immunoincompetent.

Evidentiary reference Scott (Nature Biotechnology, 2005, Vol. 23, No. 9, pages 1037-1039) teaches "Industry hopes to build on recent successes of monoclonal antibodies in oncology and inflammatory disease. But evidence is mounting that the exquisite selectivity and binding capacity of these therapeutics have unwanted side effects, particularly in autoimmune disease" (especially abstract). Scott further teaches that it may be an acceptable risk for a transplantation patient to use mAb therapy when faced with an opportunistic infection or a rare malignancy versus the risk of dying without a transplant, but that on the other hand, compared with living with an autoimmune disease, the risks of opportunistic infection or a rare malignancy could be deemed unacceptable (especially second to last paragraph of article on page 1039).

Evidentiary reference Schwartz and Kipnis (The Neuroscientist, 2002, Vol. 8, No. 5, pages 405-413) teach that the effect of treatment of autoimmune disorders should be immunomodulatory rather than immunosuppressive (especially abstract).

6. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of transplantation rejection using an aglycosylated IgG anti-CD3 antibody or antigen binding fragment thereof, does not reasonably provide enablement for treating any patient requiring immunosuppression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claim encompasses treatment of any patient requiring any form of immunosuppression. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.

The specification discloses that rodent CD3 antibodies have been used to influence immunological status by suppressing, enhancing or re-directing T cell responses to antigens, and therefore have therapeutic potential in the human for use as an immunosuppressive agent, for example, for the treatment of renal, hepatic and cardiac allografts (page 2 at lines 18-23). The specification discloses that first dose response, induced by anti-CD3 antibody administration causes elevated levels of circulating cytokines associated with CD3 antibody induced T cell activation (page 2 at lines 23-35). The specification discloses that aglycosylatin of antibodies has been described to reduce their ability to bind to Fc receptors *in vitro* in some cases, but that it is not predictable that this will be true of all antibodies (page 3 at lines 11-20). The specification discloses that it is possible to produce aglycosylated CD3 antibodies of the IgG class that retain their antigen binding specificity and do not induce T cell mitogenesis *in vitro* and induce a reduced level of cytokine release *in vivo*, while still maintaining some Fc binding ability (page 3 at lines 25-30). The specification discloses that an aglycosylated IgG1 anti-CD3 antibody was less potent in eliciting TNF production in CD3ε transgenic mice than the glycosylated antibody. However, "the mitogenicity of an antibody cannot be predicted in a straight forward fashion from the results of assays which measure Fc-Fc receptor interactions...the inability to bind to Fcγ receptors is no guarantee that an antibody will not be mitogenic" (Example 5 on pages 23-24).

Evidentiary reference Anasetti *et al* (J. Exp. Med. 172, 12/1990, pages 1691-1700) teach that non-mitogenic IgG anti-CD3 antibody in the presence of alloantigen was cable of inducing antigen-specific nonresponsiveness in unprimed human T cells, but not in memory T cells (especially abstract and last paragraph of article.)

Evidentiary reference Paul (Fundamental Immunology 2nd Edition, Raven Press, 1989, paragraph spanning pages 904-905) teaches that anti-CD3 mAb OKT3 which has been used extensively in humans eliminates all T cell function, but other mAbs such as CAMPATH, T-12 and CBL1, also used in clinical trials, have not proved as effective. Paul further teaches that OKT3 administration has been effective in reversing acute rejection episodes, but demonstrates problems in terms of not always eliminating the target T cell population. Paul teaches that the use of the OKT3 antibody represents an extremely broad, nonspecific form of immunosuppression that renders the recipient broadly immunoincompetent.

Evidentiary reference Scott (Nature Biotechnology, 2005, Vol. 23, No. 9, pages 1037-1039) teaches "Industry hopes to build on recent successes of monoclonal antibodies in oncology and inflammatory disease. But evidence is mounting that the exquisite selectivity and binding capacity of these therapeutics have unwanted side effects, particularly in autoimmune disease" (especially abstract). Scott further teaches that it may be an acceptable risk for a transplantation patient to use mAb therapy when faced with an opportunistic infection or a rare malignancy versus the risk of dying without a transplant, but that on the other hand, compared with living with an autoimmune disease, the risks of opportunistic infection or a rare malignancy could be deemed unacceptable (especially second to last paragraph of article on page 1039).

Evidentiary reference Schwartz and Kipnis (The Neuroscientist, 2002, Vol. 8, No. 5, pages 405-413) teach that the effect of treatment of autoimmune disorders should be immunomodulatory rather than immunosuppressive (especially abstract).

Evidentiary reference Phillip (Children's Hospital Quarterly, 1998, Vol. 10, No. 2, Abstract of pages 81-94) teaches that changes in the GH-IGF system in the NOD mouse model of diabetes mellitus (DM) play a major role for these growth factors in the development of diabetic nephropathy. Phillip teaches that there are differences in serum GH levels in NOD mice, which is a model of spontaneous diabetes that develops significant glomerular lesions similar to human disease, in contrast to those levels described in the STZ model of diabetes, thus indicating that the STZ model of diabetes does not as closely follow human disease.

Evidentiary reference Herold *et al* (Diabetes, 41: 385-391, 1992) teaches that the STZ model is a chemically induced model of diabetes in the mouse. Herold *et al* teach that it is of considerable clinical interest whether nonactivating forms of anti-CD3 mAbs will be effective once the immune response has been initiated (especially last sentence of article).

There is insufficient guidance in the specification as to how to use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 27 is indefinite for depending upon non-elected claim 1. Applicant is required to rewrite claim in independent form.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claim 27 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of U.S. Patent No. 6,706,265 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because "immunosuppressing graft rejection" recited in said claim 19 is a species of condition requiring immunosuppression, and the anti-aglycosylated anti-CD3 antibody recited in the said claim 19 is a species of aglycosylated anti-CD3 antibody.

12. Claim 27 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2 and 4 of U.S. Patent No. 6,5,585,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because "renal allograft rejection" recited in said claims 2 and 4 is a species of condition requiring immunosuppression, and the anti-aglycosylated anti-CD3 antibody recited in the said claims 2 and 4 is a species of aglycosylated anti-CD3 antibody.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hirsch *et al* (The Lancet, 6/89, Vol. 8651, page 1390) in view of Schlom (Molec. Cell. Res. Fut. Diagn. Ther., 1990, S. Broder Ed. , Williams and Wilkins, Baltimore, USA, pages 95-134), Tao and Morrison (J. Immunol., 1989, Vol. 143, pages 2595-2601, IDS reference) and Hirsch *et al* (J. Immunol. 2/89, Vol. 142, No. 3, pages 737-743).

Hirsch *et al* teach that administration of anti-CD3 monoclonal antibodies (mAbs), but not $F(ab')_2$ fragments of anti-CD3 antibodies, for management of organ allograft are associated with side effects that include chills, fever, pulmonary edema, and cardiovascular shock and death. Hirsch *et al* further teach that these side effects are a consequence of release of lymphokines following activation of T cells by the mAbs. Hirsch *et al* teach that morbidity from anti-CD3 could be more severe in patients with normal T cell function than it has been in transplant recipients. Hirsch *et al* teach that caution is warranted when administering anti-CD3 mAbs, including OKT3 to patients with normal or increased T cell function, in particular to autoimmune patients (see entire article).

Hirsch *et al* do not teach wherein an aglycosylated anti-CD3 antibody is administered to a patient requiring immunosuppression such as an allograft recipient.

Schlom teaches that antibody fragments such as $F(ab')_2$ fragments clear from the plasma pool at a much faster rate than the whole IgG antibody molecule, and that a lower percent injected dose is delivered *in vivo* compared to that of the intact IgG antibody, due to their breaking up into Fab' fragments *in vivo* and the subsequent rapid clearance rate from the circulation (paragraph spanning pages 97 and 98).

Tao and Morrison teach that an aglycosylated IgG1 isotype chimeric mouse-human antibody possessed the same serum half-life as the glycosylated chimeric antibody, while being deficient in ability to activate 'c and to bind human FcgRI. Tao and Morrison further teach that removal of the N-linked Asn at position 297 in the Ch2 domain of human IgG molecules by mutation of Asn^{297} to Gln or His for IgG or to Lys for IgG3 will affect aglycosylation (especially abstract, introduction and discussion sections).

Hirsch *et al* teach that mAbs against CD3, including OKT3, have been used as an immunosuppressant in the clinical setting to treat organ graft rejection (especially first paragraph of article). Hirsch *et al* further teach that the T cell activating properties of the anti-CD3 mAbs are dependent upon multivalent cross-linking of the mAbs, *i.e.,* the presence of an Fc segment that will bind to Fc receptors is necessary for T cell activation (especially abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an aglycosylated mouse-human IgG1 chimeric version of the anti-CD3 mAb taught by either Hirsch *et al* references using the methodology taught by Tao and Morrison to produce an aglycosylated antibody such as taught by Tao and Morrison that was not able to bind Fc receptors or 'c, and thus not able to activate T cells as taught by Hirsch *et al* (2/89), to produce a therapeutic antibody having a longer serum half life such as the whole IgG molecule taught by Schlom, and to have used it to treat transplantation rejection as taught by Hirsch *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make an aglycosylated antibody such as taught by Tao and Morrison using their methodology, but having specificity for binding CD3 as taught by Hirsch *et al* (either reference) in order to treat organ graft rejection as taught by Hirsch *et al* (either reference), that would not induce T cell activation because Hirsch *et al* (6/89) teach that detrimental side effects of administering whole anti-CD3 mAb is due to T cell activation, Hirsch *et al* (2/89) teach that T cell activating properties of the anti-CD3 mAbs are dependent upon the presence of an Fc segment that will bind Fc receptors, Tao and Morrison teach that aglycosylated IgG antibody is not able to bind 'c and Fc receptors, and Schlom teaches that administration of whole IgG is superior to administration of $F(ab')_2$ fragments in terms of longevity and delivery of higher amounts of therapeutic antibody.

15. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Herold *et al* (Diabetes, 3/1992, Vol. 41, pages 385-391) in view of Schlom (Molec. Cell. Res. Fut. Diagn. Ther., 1990, S. Broder Ed. , Williams and Wilkins, Baltimore, USA, pages 95-134) and Tao and Morrison (J. Immunol., 1989, Vol. 143, pages 2595-2601, IDS reference).

Herold *et al* teach that anti-CD3 mAb is effective in the suppression of organ allograft rejection in both humans and mice, but significant clinical side effects are associated with its use (especially first paragraph on page 386). Herold *et al* teach that clinical side effects are common with anti-CD3 treatment due to the ability of these mAbs to activate T cells *in vivo*. Herold *et al* teach that "the severity of these side effects is increased when anti-CD3 MoAb is administered in the nontransplantation setting such as to patients with...IDDM...As a result, the applicability of anti-CD3 therapy to autoimmune disease has been limited and little is known regarding its effects on T-cell responses in the autoimmune setting." (especially first paragraph on page 386). Herold *et al* teach that the presence of an Fc segment that will bind to Fc receptors is necessary for T cell activation *in vivo* (especially first paragraph of Discussion on page 389). Herold *et al* further teach use of whole anti-CD3 mAb or $F(ab')_2$ fragments to treat the STZ model of diabetic mouse. Herold *et al* teach that nonactivating forms of anti-CD3 mAbs may be a useful form of immunosuppressive treatment for incipient IDDM because they do not cause morbidity associated with activation of T cells, which occurs with whole mAb (especially abstract). Herold *et al* teach that it is of considerable clinical interest whether nonactivating forms of anti-CD3 mAbs will be effective once the immune response has been initiated (especially last sentence of article).

Herold *et al* do not teach wherein the nonactivating form of anti-CD3 mAb is an aglycosylated anti-CD3 mAb.

Schlom teaches that antibody fragments such as $F(ab')_2$ fragments clear from the plasma pool at a much faster rate than the whole IgG antibody molecule, and that a lower percent injected dose is delivered *in vivo* compared to that of the intact IgG antibody, due to their breaking up into Fab' fragments *in vivo* and the subsequent rapid clearance rate from the circulation (paragraph spanning pages 97 and 98).

Tao and Morrison teach that an aglycosylated IgG1 isotype chimeric mouse-human antibody possessed the same serum half-life as the glycosylated chimeric antibody, while being deficient in ability to activate 'c and to bind human FcgRI. Tao and Morrison further teach that removal of the N-linked Asn at position 297 in the Ch2 domain of human IgG molecules by mutation of Asn^{297} to Gln or His for IgG or to Lys for IgG3 will affect aglycosylation (especially abstract, introduction and discussion sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an aglycosylated mouse-human IgG1 chimeric form of the anti-CD3 mAbs taught by Herold *et al* using the methodology of Tao and Morrison to make a more effective therapeutic agent than the $F(ab')_2$ fragments taught by Schlom or by Herold *et al* and to have used it to treat a patient having an organ transplant as taught by Herold *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a nonactivating anti-CD3 mAb therapeutic agent for use in organ transplantation as taught by Herold *et al*, but instead of making the $F(ab')_2$ fragments taught by Herold *et al*, to make an aglycosylated version of the whole mAb as taught by Tao and Morrison because Schlom teaches that whole IgG antibody is more effective in terms of having a longer half life in circulation and being delivered in higher amounts than are the $F(ab')_2$ fragments, and Tao and Morrison teach that the aglycosylated IgG antibodies will not bind to Fc receptors and thus will not activate T cells to produce morbidity and mortality as taught by Herold *et al*.

16. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Routledge *et al* (Eur. J. Immunology, 1991, Vol. 21, pages 2717-2725, IDS reference) or Applicant's admitted prior art (on page 3 at paragraph 1) in view of Tao and Morrison (J. Immunol.,1989, Vol. 143, pages 2595-2601, IDS reference).

Routledge *et al* teach a humanized anti-CD3 antibody and its use as immunosuppressive agent in human where the destruction of T cells is desirable (especially introduction and last two paragraphs of article). Routledge *et al* teach that T cell activation using non-humanized anti-CD3 antibody is caused by T cell activation mediated by T cell/monocyte crosslinking via the anti-CD3 binding to Fc receptors on macrophages (especially Introduction). Routledge *et al* teach that humanization is used to reduce the non-human component so a significant anti-globulin response is unlikely to occur (especially Introduction).

The admitted prior art on page 3 at paragraph 1 discloses that humanized anti-CD3 antibodies are known in the art.

Neither Routledge *et al* nor the admitted prior art teach an aglycosylated anti-CD3 antibody.

Tao and Morrison teach that an aglycosylated IgG1 isotype chimeric mouse-human antibody possessed the same serum half-life as the glycosylated chimeric antibody, while being deficient in ability to activate 'c and to bind human FcgRI. Tao and Morrison further teach that removal of the N-linked Asn at position 297 in the Ch2 domain of human IgG molecules by mutation of Asn^{297} to Gln or His for IgG or to Lys for IgG3 will affect aglycosylation (especially abstract, introduction and discussion sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an aglycosylated version of the anti-CD3 antibody taught by Routledge *et al* or the admitted prior using the methodology taught by Tao and Morrison and to have used the resulting antibody to as an immunosuppressant as taught by Routlege *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a therapeutic agent that is useful for treating transplantation rejection as taught by Routledge *et al* using an aglycosylated antibody as taught by Tao and Morrison that lacked effector functions that are deleterious as taught by Routledge *et al*.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino

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February 3, 2006

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